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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/088,780	SECOMBES ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 21-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 21-54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 March 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6/25/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

DETAILED ACTION

Claims 1-18 and 21-54 are pending and considered.

Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically the application fails to comply with CFR 1.821(d), which states:

(d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing " in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO: " in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

The specification discloses nucleotide and amino acid sequences on pages 9-10. However, these sequences are not identified by sequence identifiers in the brief description of the figures.

For compliance with sequence rules, it is necessary to include the sequence in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a sequence, i.e., as a string of particular bases or amino acids, and that otherwise meets the criteria of 37 CFR 1.821(a), must be set forth in the "Sequence Listing." (see MPEP 2422.03).

For the response to this office action to be complete, Applicants are required to comply with the Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Priority

If applicant desires priority under 35 U.S.C. 119(a-d, f) based upon a previously filed application, specific reference to the earlier filed application must be made in the instant application. For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph unless it appears in an application data sheet. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No. _____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior

application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

Drawings

The drawings are objected to because drawing 1 is not labeled "FIGURE 1". A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Claim Objections

Claim 41 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 41 further comprises a secretion sequence, while the claim from which it depends comprises a secretion sequence.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 33, 38, and 41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

With regard to Claims 14, 33, and 38, the limitation "two amino acids substitutents in the H-chain gene respectively" is unclear.

With regard to Claim 41, the metes and bounds of the limitation "further comprises a gene sequence encoding a secretion signal" is unclear, as the Claim from which it depends, Claim 38, comprises a secretion signal. It is not clear how Claim 41 further limits Claim 38.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 21-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for protection of a fish against viral haemorrhagic septicaemia virus (VHSV) comprising a non-infectious DNA nucleic acid construct encoding the single chain antibody 3F1H10 that recognizes VHSV, the DNA sequence for the antibody listed on pages 9-10 of the specification and which comprises substitutions of asparagines 35a with threonine and lysine 64 with threonine and is linked at the 5' end to the secretion signal of transforming growth factor beta, and which sequences is operably linked to

the CMV promoter and a polyA tail for protecting a fish against VHSV infection, and vaccines comprising such compositions, and methods of providing prophylactic treatment of fish against VHSV by the administration of these compositions, by injection into the epaxial muscles below the dorsal fin, which compostions transform cells of the muscle tissue local to the injection site and produce secreted 3F1H10 antibodies, thereby producing protection against VHSV, does not reasonably provide enablement for any nucleic acid construct encoding any antibody, any secretion sequence, any promoter sequence, any form of administration, any form of composition, treatment of any animal, or any form of treatment to any agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

The Breadth of the Claims

Claims 1-18 and 21-54 are broad in scope. The following paragraphs will outline the full breadth of these claims.

Claims 1-18 encompass any composition for protection of any animal against any disease-causing agent, the composition comprising any non-infectious nucleic acid construct encoding any recombinant antibody to the agent. Claim 2 limits the animal to which protection may be conferred to any mammal or any fish. Claim 3 limits the animal to having any deficiency in its immune system. Claim 4 limits the disease-causing agent to any pathogen, any allergen, or any toxic substance. Claim 5 limits the protection to prophylactic protection. Claim 6 limits the recombinant antibody to being derived from any antibody raised against the disease causing agent. Claim 7 limits the encoded recombinant antibody to comprising heavy and light chain genes linked by any linker sequence. Claim 8 limits the nucleic acid construct to further comprising any sequence encoding any secretion signal peptide. Claim 9 limits the composition to further comprising genes encoding any antibody molecules to several different epitopes of the agent. Claim 10 limits the composition to comprising a library of genes encoding antibodies to the disease agents. Claim 11 limits Claim 10 to a library of single-chain antibodies. Claim 12 limits the composition of Claim 1 to encoding any virus-neutralizing antibody. Claim 13 limits

Claim 12 to single-chain antibody molecules. Claim 14 limits Claim 1 to including any nucleic acid construct encoding a VHSV-neutralizing antibody, 3F1H10 comprising to amino acid substituents in the H chain, where asparagines 35a and lysine 64 are each replaced by threonines, and comprising the rainbow trout TGF-beta secretion signal linked to the 5' end of 3F1H10. Claim 15 limits the composition of Claim 6 to encoding an antibody molecule derived from any antibody raised against IgE antibodies, when the agent is an allergen. Claim 16 limits Claim 1 to DNA nucleic acid constructs. Claim 17 limits the compsition of Claim 1 to being in the form of any vaccine, any dosage form, any cream, any ointment, any liquid, or any paint. Claim 18 limits the form of administration of Claim 17 to any of injection, spray, or gene gun.

Claims 21-37 encompass any composition for protection of any animal against any disease-causing agent, comprising any non-infectious nucleic acid construct encoding any recombinant antibody to the agent, wherein the encoded antibody comprises any domains of the Ig heavy and light chains linked by any linker sequence. Claim 22 limits the animal to which protection may be conferred to any mammal or any fish. Claim 23 limits the animal to having any deficiency in its immune system. Claim 24 limits the disease-causing agent to any pathogen, any allergen, or any toxic substance. Claim 25 limits the protection to prophylactic protection. Claim 26 limits the recombinant antibody to being derived from any antibody raised against the disease causing agent. Claim 27 limits the nucleic acid construct to further comprising any sequence encoding any secretion signal peptide. Claim 28 limits the composition to further comprising genes encoding any antibody molecules to several different epitopes of the agent. Claim 29 limits the composition to comprising a library of genes encoding antibodies to the disease agents. Claim 30 limits Claim 29 to a library of single-chain antibodies. Claim 31 limits

the composition of Claim 21 to encoding any virus-neutralizing antibody. Claim 32 limits Claim 31 to single-chain antibody molecules. Claim 33 limits Claim 21 to including any nucleic acid construct encoding a VHSV-neutralizing antibody, 3F1H10 comprising to amino acid substituents in the H chain, where asparagines 35a and lysine 64 are each replaced by threonines, and comprising the rainbow trout TGF-beta secretion signal linked to the 5' end of 3F1H10. Claim 34 limits the composition of Claim 26 to encoding an antibody molecule derived from any antibody raised against IgE antibodies, when the agent is an allergen. Claim 35 limits Claim 21 to DNA nucleic acid constructs. Claim 36 limits the compsition of Claim 21 to being in the form of any vaccine, any dosage form, any cream, any ointment, any liquid, or any paint. Claim 37 limits the form of administration of Claim 36 to any of injection, spray, or gene gun.

Claims 38-43 encompass any composition for protection of a fish against any disease causing agent, comprising any non-infectious DNA encoding monoclonal antibody 3F1H10 with two substitutions: asparagines 35a and lysine 64 each replaced by threonine, and rainbow trout TGF-beta linked to the 5' end of the antibody encoding sequence. Claim 39 limits the protection to prophylactic. Claim 40 limits the encoded molecule to comprising variable domains of the light and heavy chain genes, linked together by any linker sequence. Claim 41 limits the nucleic acid construct to further comprising a sequence encoding any secretion sequence. Claim 42 limits the form of the composition to any vaccine, any dosage form, any cream, any ointment, any liquid, or any paint. Claim 43 limits the administration of Claim 42 to by any of injection, any spray, or any gene gun.

Claims 44-45 and 51-53 encompass any method of treating any animal comprising administering to the animal any composition encompassed by Claim 1. Claim 45 limits the

composition to mediating expression of any recombinant antibody to the agent. Claim 51 limits the animal to any fish or any aquatic animal. Claim 52 limits the animal to any mammal. Claim 53 limits the mammal to humans.

Claim 46 encompasses any method of treating any animal comprising administration of any composition encompassed in Claim 3.

Claim 47 encompasses any method of treating any animal comprising administration of any composition encompassed by Claim 6.

Claim 48 encompasses any method of treating any animal comprising administration of any composition encompassed by Claim 21.

Claim 49 encompasses any method of treating any animal comprising administration of composition encompassed by Claim 38.

Claims 50 and 54 encompass methods of treating any animal with any congenital or acquired immunodeficiency, comprising administering of more than one non-infectious nucleic acid construct encoding any antibodies against any spectrum of any disease-causing agents. Claim 54 limits the animal to humans.

Because these claims are broad, encompassing compositions and the use of such compositions for treating any animal for any disease-causing agent by the administration of a wide range of nucleic acids encoding any antibody or antibodies, without limitation to forms of aministration or regulatory constructs, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge, to a reasonably comprehensive extent. In other words, each of those aspects considered broad must be fleshed out to a reasonable extent so that one of ordinary skill in the art at the time of invention by Applicant

(hereinafter the "Artisan"), would be able to practice the invention, and do so to the fully-claimed scope of invention, without an undue burden being imposed on such Artisan (undue burden). However, as will be discussed below, this burden has not been met.

The Nature of the Invention

The invention is in the nature of compositions for, and methods of performing, gene therapy to treat animals against disease-causing agents.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many

of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Moreover, because Applicant claims so many forms of nucleic acid, each of these forms must be shown to integrate successfully and produce recombinant antibody *in vivo*. One of skill in the art would recognize that each form, single stranded and double stranded and DNA and RNA would have their own mechanisms of incorporation, and such would need to be reasonably predictive to produce transformation of the cells in high enough numbers and produce the protein

in large enough amounts for a long enough period of time to produce a therapeutic effect, which effect may be different if the treatment is prophylactic or after being exposed to any disease causing agent. Treatment would be different because once exposed, the agent has already begun effecting the animal, and therefore not only inhibition of further effects must be accomplished, but removing previously-begun effects must be accomplished.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, encoding specific GDNF proteins, under the control of specific promoters and other control elements, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements.

The State of the Prior Art

As Applicant states in the specification (p. 18, lines 14-17), there is no art of record demonstrating the establishment of protective immunity to any infectious pathogen in higher vertebrates by administration of genes encoding pathogen-specific sing chain antibodies. However, there exists some art the administration of antibody or antibody-fragment encoding genes as therapy for infectious diseases. Such genes are generally referred to as "intrabodies", as reviewed with respect to antiviral agents (one pathogen type), by Marasco (2001) Curr. Topics

Microbiol. Immunol., 260 : 247-70. However, Marasco does not enable, but in fact raises concerns that the Artisan would have with regard to Applicants invention.

Specifically, Marasco is directed to recombinant antibody genes that are expressed intracellularly, and hence do not enable those applications of such genes that are secreted after expression (p. 247, first paragraph). Moreover, with regard to these genes, no *in vivo* studies have been reported, and CTL responses against transduced cells is likely to prohibit their use (p. 253, first full paragraph; p. 264, first full paragraph). Also, one of skill in the art would recognize that multiple genes encoding multiple recombinant antibodies would amplify all of these problems mentioned in the nature of the invention and here. Therefore, one of skill in the art would not only have those issues mentioned in the nature of the invention (above) to consider, but would also need to be able to reasonably predict that CTL responses would not diminish the protective immunity conferred by the administration of the compositions of Applicant's claims.

Hence, the prior art is not only as non-enabling of Applicant's invention as the nature of the invention, but more so, because of the possibility of CTL responses removing any protective effect before it can be established. Hence, because the art is lacking in any examples of nucleic acids encoding any recombinant antibody that is secreted, and due to the problems mentioned above with regard to gene therapy, each of which are amplified by the use of multiple recombinant antibodies, absent a largely enabling disclosure by Applicant, by way of specific direction and guidance and examples, the invention claimed by Applicant is not enabled for its full scope.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, is not enabling for new genes encoding monoclonal or polyclonal recombinant antibody compositions and any treatment against disease-causing agents with the same, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any therapeutic application.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

The Amount of Direction and Guidance Provided by Applicant

The specification broadly discusses RNA and DNA constructs encoding antibodies or antibody fragments and their use in conferring protection to any animal against pathogens, allergens, and toxins (p. 1). Further broad discussion is given to passive immunization, *in vitro* production of antibodies, objects of the invention tracking the claims, a broad belief that the antibodies encoded will act as naturally-occuring host antibodies to confer protection, by binding cells that have been infected by viruses or the viruses themselves, and inhibiting the virus and/or giving the host time to mount an immune response (pp. 1-4). More broad discussion is given to expression vectors, the antibody fragments, a long list of non-comprehensive pathogens, use in

immunodeficient humans, allergic reactions and antibodies to IgE, signal sequences, identification sequences, methods of administration, epitopes of the antibodies, and therapeutic compositons (pp. 4-8).

However, such broad discussion does not constitute the specific guidance and direction that would allow the Artisan to predict that any specific recombinant antibody, any form of nucleic acid, any disease-causing agent, any animal, any regulatory sequences, or any form of administration could be used for treatment of any specific condition. The Artisan could not reasonably predict, as reviewed in the nature of the invention and state of the prior art, that enough nucleic acid would reach the target tissue, transform the target tissue, produce enough stable and functional mRNA, and proteins therefrom, and the protein would be stable and functional, and processed correctly, to produce enough of an effect, for a long enough period of time to effect any specific treatment, and, moreover, that CTL responses would not nullify any such effects.

Because of the lack of guidance and direction that would assure the Artisan of the efficacy of such treatments, the examples would be required to provide a very strong showing of effectiveness. Absent this strong showing in the examples, it would have required undue experimentation to make and/or use the invention within its fully claimed scope.

The Existence of Working Examples

Applicant provides one Example, divided into many parts. Each of these parts will be reviewed sequentially as separate example numbers. Example 1 demonstrates the making of a plasmid vector comprising single chain antibodies. Example 2 demonstrates injection of plasmids of example 1 into fish, into the epaxial muscles below the dorsal fin. Example 3

demonstrates an analysis of the expression of single-chain antibodies in the muscle tissue at the site of injection in example 2. Example 4 demonstrates sampling of the blood plasma from the fish injected in example 2. Example 5 demonstrates that tissue-cultures and plasma samples from fish, each transfected with the plasmids in example 2, exhibit virus neutralizing activity against virulent VHSV. Example 6 demonstrates the protocol used to determine immunoprotection of fish injected in example 2. Example 7 demonstrates single chain antibodies could be detected in the samples collected in example 5. Example 8 demonstrates that cell cultures expressing the single-chain antibodies exhibited better suvival than those not expressing the recombinant antibodies. Example 9 demonstrates the plasma collected in example 4 from fish transformed with the plasmid encoding an antibody expressed the antibody. Example 10 demonstrates that fish transfected with the antibody-encoding plasmid exhibited 81% survival, versus 6% for null-plasmid transfected fish, when challenged with virulent VHSV.

Moreover, it is noted that in these examples, the only plasmid encoding any recombinant antibody is a double-stranded DNA plasmid encoded the single-chain antibody 3F1H10, which has 2 mutations, amino acids 35a and 64 are each substituted with threonine, with the rainbow trout TGF-beta secretion sequence at its 5' end, and driven by the CMV promoter (p. 11, lines 21-30).

As noted above, in the nature of the invention, this is one example of a specific embodiment which, by way of example, must have met all the requirements to effect prophylactic treatment. However, such examples do not enable other embodiments, due to the reasons given above, in the nature of the invention and state of the prior art. To wit, the Artisan could not reasonably predict in view of the disclosure that multiple antibody genes could be

used, any agent could be treated, such treatment could be effected after exposure to the agent, such nucleic acids, of any type of promoter could be used, any type of antibody could be used, or any animal could be treated.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the insufficiency of the working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, the Artisan would have been required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope.

Such experimentation would be required to determine which forms of nucleic acid could be used, which agents could be treated, which animals could be treated, which form of administration could be used, which types of treatment could be effected, which secretion sequences to use, whether to use a secretion sequence, whether multiple genes could be used, which promoters would be required, which immune system deficiencies could be treated, if any, and whether such treatments would produce enough transformed cells that produce enough stable and functional RNA and proteins therefrom, for a long enough period of time to effect treatment.

Conclusion

Because of the large amount of experimentation required to make and/or use the invention within its fully claimed scope, such experimentation is considered undue, and therefore, such claims are not enabled for any animal, any antibody, any promoter, any form of nucleic acid, any form of composition, any form of treatment, any form of administration,

multiple antibody encoding genes, any secretion sequence, the absence of a secretion sequence or treatment of animals with deficient immune systems.

BECAUSE OF THE BREADTH OF THE CLAIMS, THE FOLLOWING REJECTIONS ARE HELD, EVEN IN LIGHT OF THE SCOPE OF ENABLEMENT

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 9, 12-13, 16-18, 21-27, 31-32, 35-37, and 44-54 are rejected under 35 U.S.C. 102(b) as being anticipated by WPIO Doc. No.: WO 96/37234 to Duan, et al., Filed 23 May 1996, Published 28 November 1996.

With regard to Claims 1, 7, 21, 44, and 48, Duan teaches gene therapy by administering a gene that encodes an antibody that binds an antigen associated with a disease (disease causing agent) (ABSTRACT; p. 22, lines 12-29). Moreover, Duan teaches that such administered compositions preferably are in the form of non-cytopathic eukaryotic viruses (non-infectious nucleic acids) (p. 17, lines 18-22). Furthermore, the antibody may comprise variable heavy and light chains, joined by a linker (p. 14, lines 19-32).

With regard to Claims 2, 22, and 51-53, Duan teaches treating fish and mammals and humans (p. 10, lines 14-17).

With regard to Claim 3, 23, and 46, because Duan teaches treating diseases after such diseases have taken effect, as well as treating HIV infection, (p. 4, lines 6-18), and because the major effect of HIV is immune system deficiency, Duan inherently teaches use in animals with deficient immune systems.

With regard to Claim 4, 24 and 45, the disease causing-agent may be a pathogen, e.g., viruses (p. 2, line 3-p. 3, line 23).

With regard to Claim 5 and 25, the compositions may be administered prophylactically (p. 20, lines 7-13).

With regard to Claim 6, 26, and 47, the antibody may be derived from an antibody raised against the disease-causing agent (p. 14, lines 19-32).

With regard to Claim 9 and 28, Duan teaches that multiple antibodies to different epitopes may be used (p. 22, line 30-p. 23, line 9).

With regard to Claim 12 and 31, Duan teaches a virus-neutralizing antibody (EXAMPLE 23).

With regard to Claim 13 and 32, the antibody is a single-chain molecule (EXAMPLE 23).

With regard to Claim 16 and 35, Duan teaches a DNA form of vector (p. 43, lines 5-8).

With regard to Claim 17 and 36, Duan teaches intravenous, perfusion, and topical treatment (p. 17, lines 15-18), which encompasses at least liquids, ointments, and paints.

With regard to Claim 18 and 37, Duan teaches intravenous, perfusion, and topical treatment (p. 17, lines 15-18), which encompasses at least injection.

With regard to Claim 50, Duan teaches gene therapy by administering a gene that encodes an antibody that binds an antigen associated with a disease (disease causing agent) (ABSTRACT; p. 22, lines 12-29). Moreover, Duan teaches that such administered compositions preferably are in the form of non-cytopathic eukarytoc viruses (non-infectious nucleic acids) (p. 17, lines 18-22). Furthermore, Duan teaches that multiple antibodies to different epitopes may be used (p. 22, line 30-p. 23, line 9), and because Duan teaches treating diseases after such

diseases have taken effect, as well as treating HIV infection, (p. 4, lines 6-18), and because the major effect of HIV is immune system deficiency, Duan inherently teaches use in animals with deficient immune systems.

With regard to Claim 54, Duan teaches treating humans (p. 10, lines 14-17).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 8, 15, 21, 27, and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,543,144 to Chang, filed 21 January 1993; date of patent 6 August 1996.

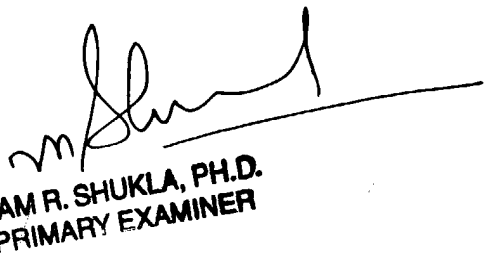
With regard to Claims 1, 15, 21 and 34, Chang teaches treating allergies with anti-IgE antibodies (TITLE; ABSTRACT). Moreover, Chang teaches preparing plasmid vectors encoding the recombinant antibodies. Furthermore, Chang teaches the antibodies may be single chain antibodies, comprising the heavy and light chain variable regions, separated by a linker (col. 10, line 63-col. 11, line 8).

With regard to Claims 8 and 27, because Chang teaches secreted and membrane bound forms of the antibody, Chang inherently teaches such plasmid vectors comprising a secretion signal, otherwise the secreted form of the antibody could not be made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

Continuation of Attachment(s) 6). Other: Notice to Comply With Sequence Rules.